

Choosing the Most Suitable Non-Viable Sample Point Locations

Environmental system designers are often asked where to place sample points for non-viable particle monitoring performed in a pharmaceutical cleanroom or clean device (RABS, isolator, etc.). The location of the monitoring points should be based upon a formal risk assessment using data from the certification and qualification testing. Other factors, such as equipment interference, mounting points, and operator impedance, contribute to selecting the final location for the sample probe.

Particle counting in pharmaceutical applications can be clearly segregated into one of three categories:

- Certification
- Qualification
- Monitoring

Certification is measuring a cleanroom for a standard. The only standard recognized worldwide is ISO14644-1, which defines how a cleanroom performs and its ability to show uniformity across the entire space. This is done irrespective of the activities performed in it.

Qualification is the process of analyzing risk assessment for the activities in the room. Qualification follows grid methodology testing methods. Particle counts are measured in both operational and at-rest states; however, the operational data is the most valid.

Monitoring is the ongoing sampling of the cleanroom on a frequency relative to the degree of control required to prove management over risk to finished product. The number of sample points and their location is determined by risk assessment and the finding of the qualification and certification process.

Each category requires a different approach. Using the example of a filling machine inside a Grade A room, surrounded by a Grade B area, this paper gives you steps to determine the best sampling point locations.

The frequency of sampling should reflect the risks and follows from the FDA guidance on sterile manufacture and the EC GMP Annex 1 guide. Particle monitoring should be automated and maintained in a continuous state while glassware or product is exposed.

Certification

As mentioned above, cleanroom certification is based on ISO14644-1 standards. The specifics of the assessment may vary slightly for FDA or EU GMP regulations, but the underlying methodology is

standard.

Cleanroom certification demonstrates that the entire area meets a specific ISO classification. That is, irrespective of the final use of the room, the design and implementation of the filtration system are considered. The international standard means that a cleanroom tested to meet compliance for ISO 5 standards will meet that standard independent of geography and regulatory aspects (i.e.: FDA or EU GMP). This provides a universal standard to show that a cleanroom level has been established.

There are many different resources to prove ISO compliance and this paper will not cover these in depth. However, using the example of a classic filling machine (Grade A) within a Grade B background area, the basic rules of testing can be demonstrated.

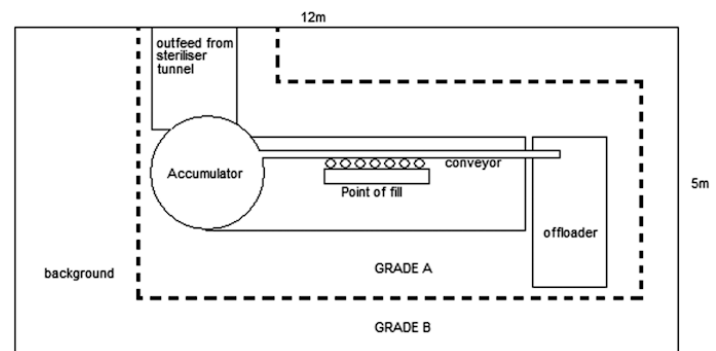


Figure 1. Filling machine in a Grade A room with a Grade B area

1. The number of sample points is based on the area:
 - a. Calculate the area of Grade A.
 - b. Calculate the area of Grade B.
2. Sample point placement for the Grade A area:
 - a. The sample points must all be equidistant and at work height, irrespective of the activity at the location of their placement.
 - b. Samples are taken in a grid pattern at the identified locations.
 - c. PASS/FAIL criteria are calculated for ISO and EC GMP Annex 1. It is recommended to have both sets of data as the FDA requires ISO14644-1 and the EC require Annex 1 data points (although the EC data would suffice for the FDA).
3. Sample point placement for the Grade B area:
 - a. Repeat the steps used for the Grade A area.
 - b. It may be more difficult to determine the locations of the samples points due to the

unusual shape of the room. An equal area formula can be done, i.e., 1 sample for every $n \text{ m}^3$.

4. A final report is created and marks the end of the certification phase.

Qualification

The qualification phase considers the risks to the quality of the finished product. Each activity must be considered and measured. Continuing with the example of the filling line, let us consider the accumulator table at the exit of the sterilizer tunnel. The risk is that glassware (vials/bottles) is exposed to the open environment. Therefore, contamination can fall into clean vials/bottles prior to filling. Operator intervention and moving glassware cause turbulent air movement on the table, impacting contamination risk to the exposed vials/bottles. It is, therefore, an area of contamination risk and the following actions should be taken.

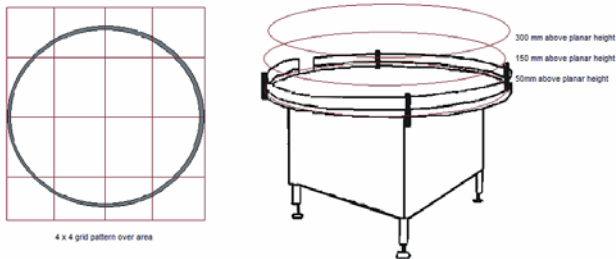


Figure 2. Applying a grid to various levels

1. Divide the area of risk into a 3 x 3 or a 4 x 4 grid. If the activity can occur at several levels then each level (that is, working height, +150 mm from work height and +300 mm from work height) must be considered,
2. A particle sample is taken at the centre of each of the grid squares and on each level.
3. Samples are taken during 'At Rest' and 'Operational' states. It may be required to work around an activity or operator to gain suitable data. Slight movement of sample points within the grid square is acceptable as a location is invalid if found to impede normal activities.
4. When all the samples are taken this will provide a particle map of the pharmaceutical activity.

Each of the key functions within the cleanroom (filling point, stoppering, general background activities, etc.) should be analyzed accordingly.

Monitoring

The location of the monitoring points should be based upon a formal risk assessment using data from the certification and qualification testing. Other factors, such as equipment interference, mounting points, and operator impedance, contribute to selecting the final location for the sample probe.

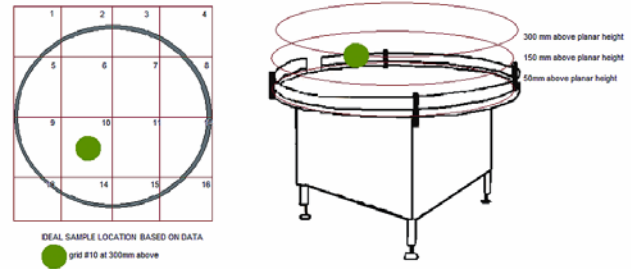


Figure 3. Ideal sample location based on data

If during a post analysis assessment of the sample point it is determined that a location is directly in line with where the operator needs to make routine system adjustments and would impede operator activities, the sample point must be moved. In such a case, the second highest ranking sample point should be selected.

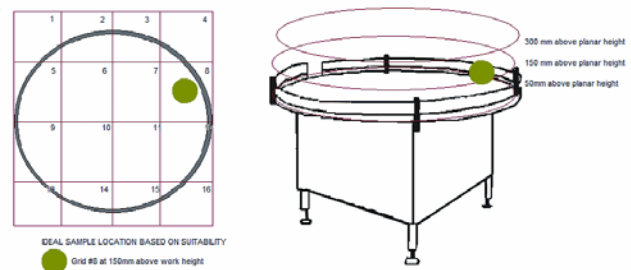


Figure 4. Ideal sample point based on suitability

The isokinetic sample probe should face into the air stream and a minimum length of tubing should be used. Although different manufacturers claim specific lengths of tubing can be used with their particle counter, this is typically a function of vacuum pump dynamics and not particle transportation. Particles of $0.5 \mu\text{m}$ move freely in long lengths of tubing. However, $5.0 \mu\text{m}$ particles do not have this same mobility. As $5.0 \mu\text{m}$ particles are a greater concern, the tubing should be maintained at shortest possible lengths.

Particle Measuring Systems quotes maximum tubing lengths based upon the same conditions of airflow and has a recommended maximum length of 3 m. However, for pharmaceutical particle systems we advise a reduced recommended length of 2 m to ensure transportation of the larger particles.

The frequency of sampling should reflect the risks and follows from the FDA guidance on sterile manufacture and the EC GMP Annex 1 guide. Particle monitoring should be automated and maintained in a continuous state while glassware or product is exposed.

Author: Mark Hallworth

© 2011 Particle Measuring Systems. All rights reserved. Reproduction or translation of any part of this work without the permission of the copyright owner is unlawful. Requests for permission or further information should be addressed to Particle Measuring Systems, Inc. at 1-800-238-1801